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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,033	10/22/2001	Patrick C. Kung	YALE-025/02US 306577-2036	9303

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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

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12/10/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/830,033	KUNG ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *83,84 and 87-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83,84 and 87-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Amendment filed 10/05/2010 is acknowledged. Claims 83,84,87-89 are pending. Claim 83 is amended to recite whole test batch and whole standardized batch.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 83,84,87-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The base claim 83 is amended to address recite whole test batch and whole standardized batch. The meaning of the term "whole batch" is not clear. Does it mean a sample of the whole plant, or a batch of all samples obtained from the plant? From applicant's arguments in this response, it seems that the "whole plant" is meant. Specification however, is open to the use of either whole plant or fractions thereof:

Examples of herbal compositions include, but are not limited to, the following components: a whole plant or a plant part of a single plant species; whole plants or plant parts of multiple plant species; multiple

components derived from a single plant species; multiple components derived from multiple plant species; or any combination of these various components

p. 20, second paragraph.

Please clarify via clearer claim language.

Claim Rejections - 35 USC § 103

Claims 83,84,87-89 remain rejected under 35 U.S.C. 103(a) as unpatentable over McLaughlin (Drug Information Journal, vol. 32, pp 513-521, 1998) and Khwaja et al (US Patent 6113907) in view of Kojima et al. (Biol. Pharm Bull, 21(4),426-428; reference provided in IDS), Wallace et al (Molecular Medicine Today. Volume 3, Issue 9, September 1997, pages 384-389), Friend et al (US Patent 6,218,122), and Xiong et al. (Molecular Breeding 4: 129–136, 1998).

The claims are directed to quality control method for assessing the equivalency of a test and standardized batches a herbal composition by exposing a biosystem (e.g., cells, or tissue, or an organism) to either standardized or test batches of the herbal composition, determining differential gene expression in the biosystem (as compared to untreated control), and comparing the differential gene expression values obtained for the test and standardized batches.

McLaughlin et al. teach that bioassays offer a special advantage in the standardization and quality control of heterogeneous botanical products. Such products can be "heterogeneous" due to the presence of mixtures of bioactive components either

from the same or from purposefully mixed botanical sources. McLaughlin describes several bioassays, such as brine shrimp lethality test, inhibition of crown gall tumors assay, inhibition proliferation assay, etc. (see Abstract), relative potency of the test *vs.* control herbal composition was determined (see, for example, p. 522 describing seasonal variations in the potency of botanical preparation).

McLaughlin does not teach using genomic-based bioassay to determine the effect of a herbal composition, and does not specifically address control samples as "standardized".

Khwaja et al teaches method for quality control of herbal compositions by fingerprinting effects of herbal compositions in bioassays to provide reproducible material in the predictable and consistent treatment of patients (column 2, lines 39-51). The reference teaches that use of bioassays is necessary for ensuring quality of a botanical product.

> Complex plant materials and extracts exist which have potent, but relatively unpredictable, medicinal properties. These materials are, for the most part, useless in a clinical setting because of the inherent risks involved with treating patients with poorly characterized materials which have no established batch consistency and which may differ widely in composition. Accordingly, there is a need to provide methods for standardizing such complex botanical materials

The method of Khwaja et al. comprises harvesting botanical material (whole or part), determining standardized bioactivity profile, comparing the calculated bioactivity of the botanical composition to a bioactivity fingerprint standard, and determine whether the botanical material is a pharmaceutical grade St. John's Wort (column 9, bottom). The "biosystems" (as they are addressed in the instant claims) in Khwaja can be selected by an artisan depending on the nature of fingerprint desired; for example, they can be

cells, tissues, or whole organisms (see cols 22, section 5.4; col.23, lines 24-26; col. 2, section 5.4.2). The herbal compositions tested are derived from a whole plant or parts thereof (see col. 16, line 51), and overall activity of the preparation is determined (col. 16, line 60). If the quantitative fingerprint of the sample falls within the range of quantities set forth for the pharmaceutical grade fingerprint, then the material is identified a pharmaceutical grade (col. 17, lines 46-49).

Thus, Khwaja reads on assessing the equivalency of a test and standardized batches a herbal composition by exposing a biosystem (e.g., cells, or tissue, or an organism) to either standardized or test batches of the herbal composition, assaying reaction of the biosystem, and comparing the quantitative measures of the response of the biosystem to the test and standardized batches.

Khwaja, as McLaughlin, does not teach "genomic-based" bioassay. However, Khwaja addresses determining differential expression of proteins, such as assaying decreased expression of reverse transcriptase in cell culture (col. 26, section 5.4.4). [1] Unlike the instant method, Khwaja addresses differential expression of a protein, rather than of a gene.

Kojima et al. teach determination of differential expression of genes resulting from exposure of "biosystem" (mice) to a Japanese herb preparation (see Abstract , p. 426) .

[1] Similarly, Hylands et al (US 6806090) teaches method for quality control and standardization of medicinal plant products comprising preparing solutions or extracts of standard and test samples of whole plant product and comparing them using one or more biological profiling techniques, such as proteomic analysis. See Example 6 describing effect of Buddleja globosa on protein expression in human dermal fibroblast cells.

The basic concept of generating and comparing expression profiles, including gene expression profiles, to known profiles for the purpose of determining drug effectiveness is well known. Wallace et al teaches that DNA chips is a major advance in testing complex mixtures which provide much faster and more reliable assay. See Abstract and throughout the reference. Friend et al (U.S. Pat. No. 6,218,122) teaches determining the effect of a drug therapy upon a subject by comparing a diagnostic gene expression profile from a subject undergoing a therapy with an "interpolated perturbation response profile" for that therapy. The interpolated perturbation response profile which is most similar to the diagnostic profile indicates the level of effect or drug dose level. Xiong et al. teaches differential gene expression profile of the whole batch of plant extract via a genomic-based bioassay. See Abstract

Taken together, using the known technique of gene array analysis of differential gene expression as a bioassay used for a quality control method instead of other types of bioassays used the methods of McLaughlin or Khwaja et al would have been obvious to one of ordinary skill. The nature of the problem to be solved – comparison between herbal compositions for the purpose of quality control may lead inventors to look at references relating to new and improved methods of assaying bioequivalence of herbal compositions. Therefore, it would have been obvious to use the more advanced method of gene expression analysis described, for example in Wallace, Xiong, or Wallace. As one skilled in the botanical art was aware of importance of understanding of gene expression for quality control, using the known technique gene

expression analysis to provide the desired information for the quality control would have been obvious to one of ordinary skill. One would have reasonable expectation of success in applying gene expression bioassay for comparison of gene expression by different batches of plant samples because gene expression was successfully utilized in determination of differential expression of plant genes resulting from exposure of "biosystem" (Kojima et al.), and differential gene expression profile of the whole batch of plant extracts (Xiong et al.) and further because Wallace et al teaches that DNA chips is a major advance in testing complex mixtures.

Response to arguments

The issue addressed by

Applicant submits that as the claim 83 was amended to positively recite a "'whole" test batch and a "whole" standardized batch", the prior art does not teach or suggest exposing a biosystem, such as cell or tissue, to a whole batch of herbal composition or the whole test batch. Response, p. 4, last paragraph. In response, the term "whole batch" is not defined in the specification and is open to interpretation as either a batch of the whole plant, or a whole batch of samples derived from the plant. Specification addresses batch of herbal composition (see p. 15, for example), and then defines a composition as comprised of a plant, plant parts, or components derived therefrom. p. 20, second paragraph. Thus, the limitation "whole" with regard to a batch, is viewed merely as comprising all samples in a batch, rather that a sample of an entire whole plant.

Conversely, the prior art does not teach "partial" (as contrasted with "whole") batches. Thus, Khwaja teaches that botanical materials are typically made from one or more plants or plant parts or extracts derived from whole plants or selected plant parts (e.g., col. 3, lines 45-60) . in particular examples, Khwaja uses whole batches derived from a part of the plant (col. 4), same as the examples of the instant invention (specification, p. 57). Applicant argues that "Khwaja does not suggest

With regard to other references, applicants have traversed the references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. It has been well established that the test for combining references is not what individual references themselves suggest but what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin,* 170 USPQ 209 (CCPA 1970). Examiner maintains that as using the gene expression as a bioassay for a quality control method instead of other types of bioassays, such as used the methods of McLaughlin or Khwaja et al, would have been obvious to one of ordinary skill in the art, it would be obvious to use the more advanced method of gene expression analysis described, for example in Wallace, Xiong, or Wallace to improve the bioassays used for plant quality control.

With regard to the Declaration under 37 CFR 1.132 filed 10/05/2010, it is insufficient to overcome the rejection under 35 U.S.C. 103(a) of record as set forth in

the last Office action because the Declaration, dated 03/2005 addresses the office action of 02/24/2004 (see paragraph #4), not the current rejection of record. With regard to expectation of success, one would have reasonable expectation of success in applying gene expression bioassay for comparison of gene expression by different batches of plant samples because gene expression was successfully utilized in determination of differential expression of plant genes resulting from exposure of "biosystem" (Kojima et al.), and differential gene expression profile of the whole batch of plant extracts (Xiong et al.) and further because Wallace et al teaches that DNA chips is a major advance in testing complex mixtures. With regard to secondary considerations, demonstration of utilization of the instant invention in Tilton publication of 2010, the evidence is not dispositive of the issue of obviousness.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571)272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin/
Primary Examiner, Art Unit 1631

mlb